Cellular shaping of fiber networks: Implications for Self-Healing and Pulmonary Fibrosis

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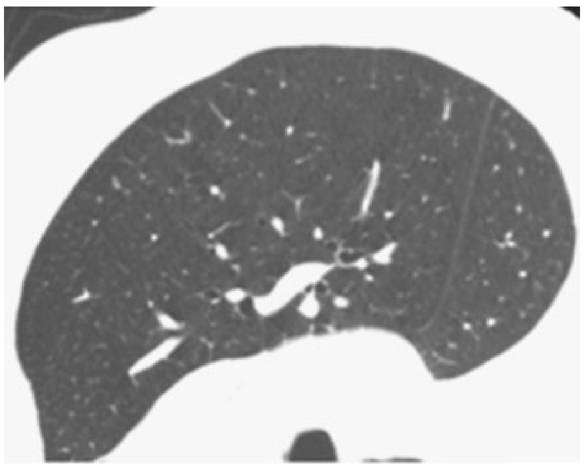
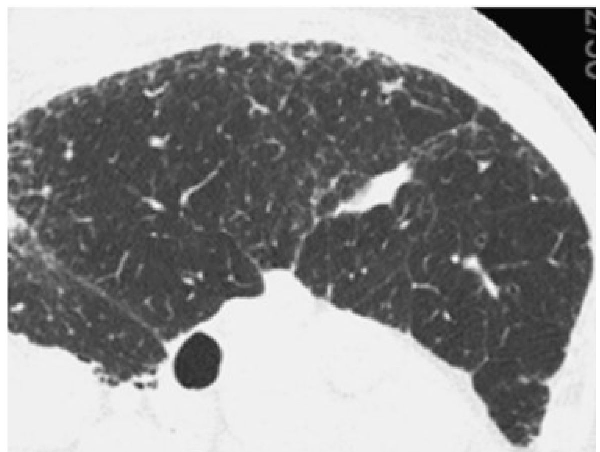
Motivation

- Idiopathic Pulmonary Fibrosis (IPF) is disease that is not curable and leads to death within 1 to 5 years.
- IPF lungs exhibit distinct progressive structural changes as a result of pathologic changes in cell behavior:
  - Subpleural Honeycombing / Cyst formation
  - Traction Bronchiectasis
  - Reduction in Lung Volume, Compliance
  - Difficulty in breathing
  - Pulmonary hypertension

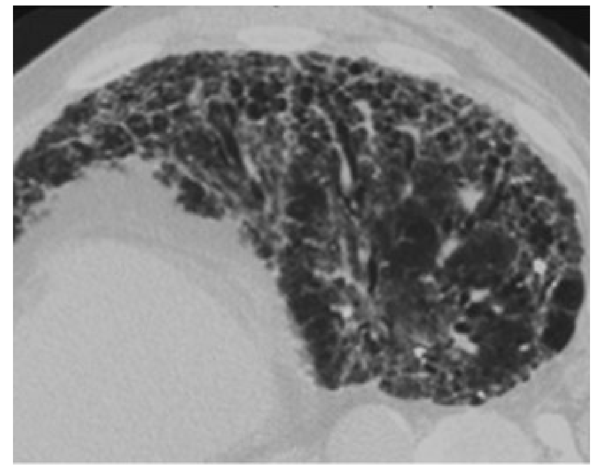
How does fibrosis look like?



Normal

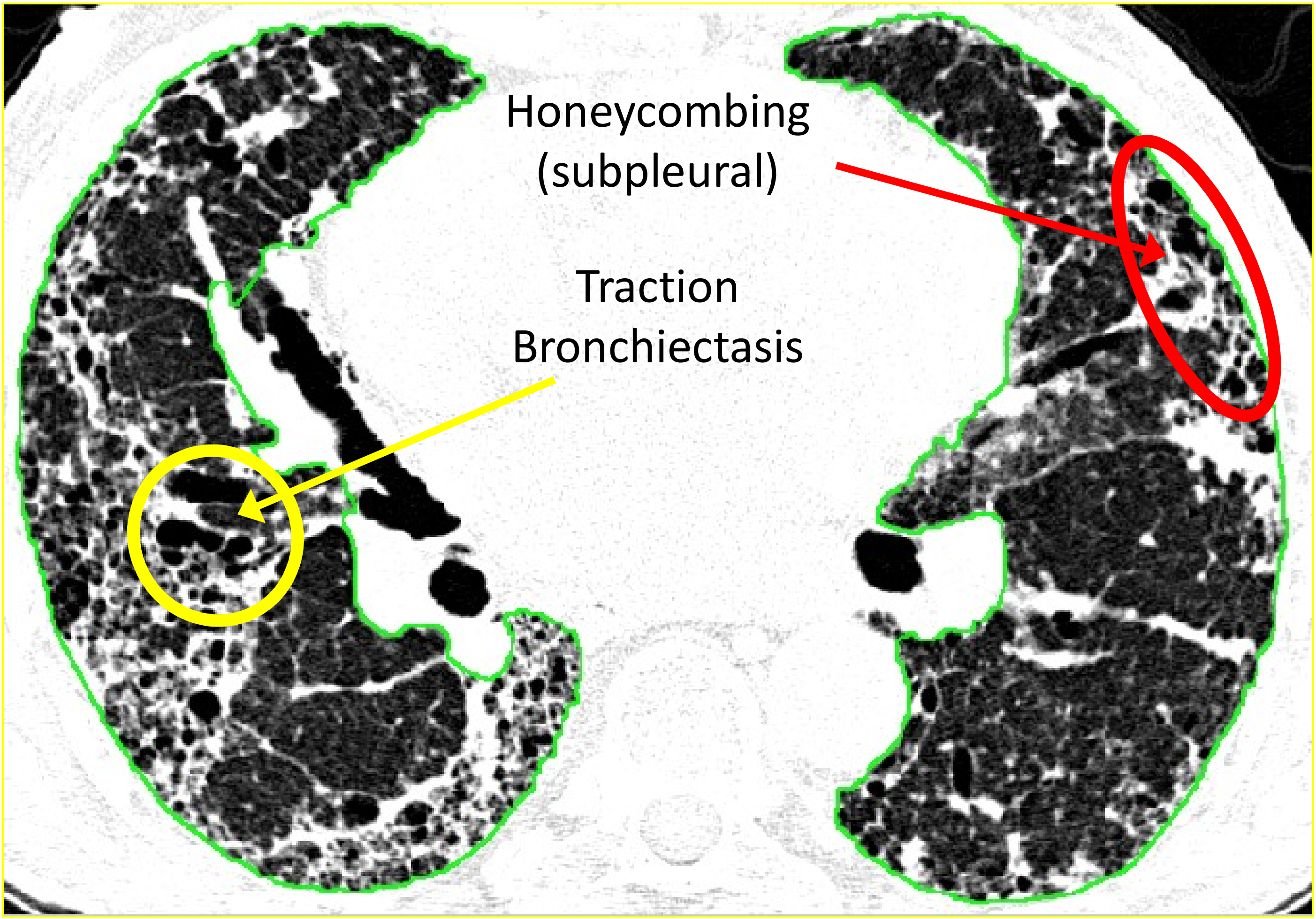


Mild fibrosis



Severe fibrosis

Topology of fibrotic changes



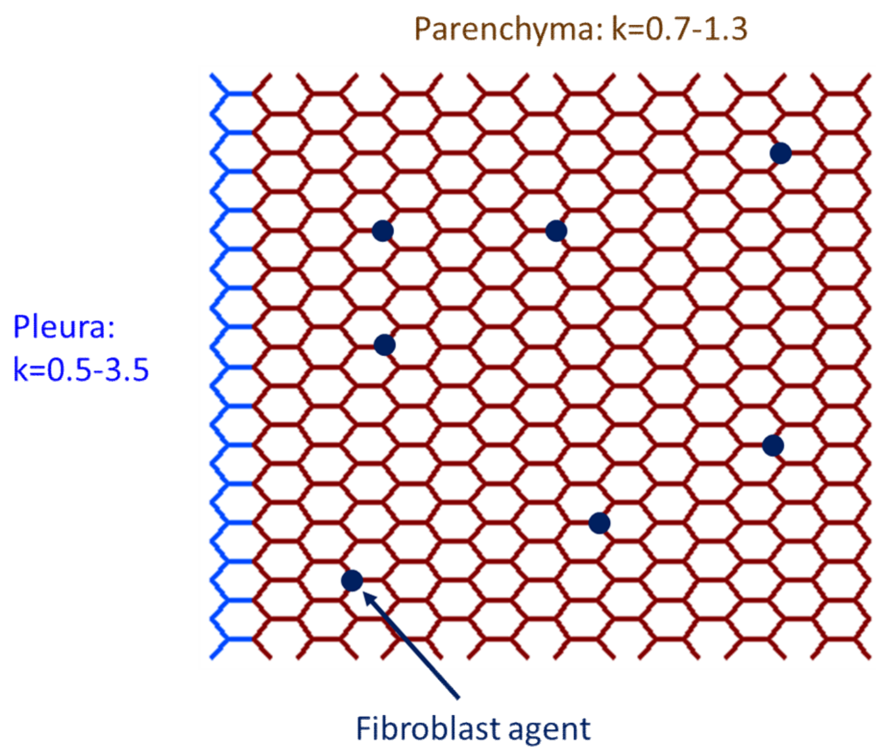
Questions

- Why does a honeycombing structure emerge under the pleura?
- How do known cell behaviors contribute to change in structure?
  - Which cell properties are important in producing key structural changes?
    - Resistance to Apoptosis
    - Collagen Deposition
    - Cell Motility / Invasiveness
    - Cell-cell interactions
    - Cell-matrix interactions
- Does tissue or cell network behavior contribute?
- Is there an interaction among the network of cells and the network of tissue elements?
  - Network of interacting cells migrate on a network of tissue elements

Hypotheses

- Properties of the pleura (higher stiffness, collagen content) prompt the initial disease process
- Activated cells migrating on the network spread fibrosis inward into the normal tissue
- Cellular processes alter network stiffness and connectivity
- Altered tissue network feeds back to cellular processes

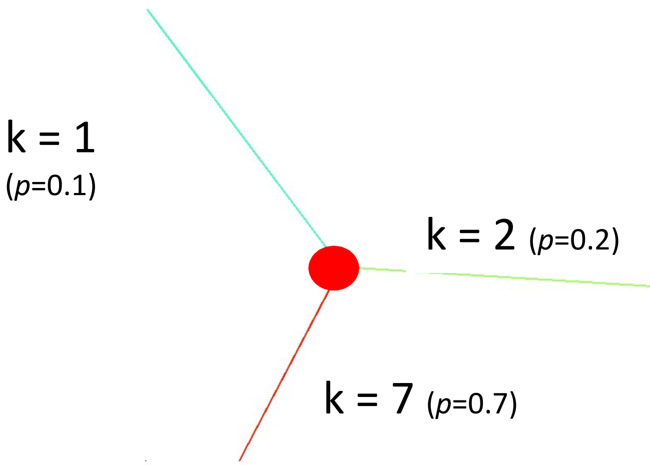
Network model and the agents



Wellman et al. Physiol. Meas. 39 064007, 2018.

Fibroblast Behavior: Migration

- Migration of human lung fibroblasts is enhanced on stiffer ECM
  - (Asano et al. Physiol Rep, 2017)
- The migration is directed toward stiffer regions
  - (Lo et al. Biophys J, 2000).
- Random walk is weighted by member stiffness



$$Probability = \frac{k}{\sum k}$$

Fibroblast Behavior: Activation

- Fibroblasts respond to stiff substrates by exhibiting myofibroblast phenotype:
  - Cells become “activated” by pathologically stiff substrates (i.e., moving across stiff members of network)
    (Parker et al., J. Clin. Invest. 2014, Brown J. Physio. 2013, Liu J. Cell Bio. 2010)
  - Cells deactivate over time when on substrates of physiologic stiffness (i.e., moving across normal members)
    (Marinkovic et al., AJRCMB 2013)

$$A = \gamma(k - k_p)$$ when agent steps on pathologically stiff (>k_p) tissue

$$A = 0.95A$$ when agent steps on normal tissue

Fibroblast Behavior: Remodeling

- Fibroblasts deposit collagen when activated:
  - Cells increase deposition of lung collagen in pulmonary fibrosis.
    - (Kirk et al. Clin Sci (Lond), 1986)
  - Cross-linking is major contributor to increased stiffness
    - (Jones et al. Elife, 2018)

$$k_{i+1} = k_i + \lambda A_i$$ when an activated agent steps on tissue wall

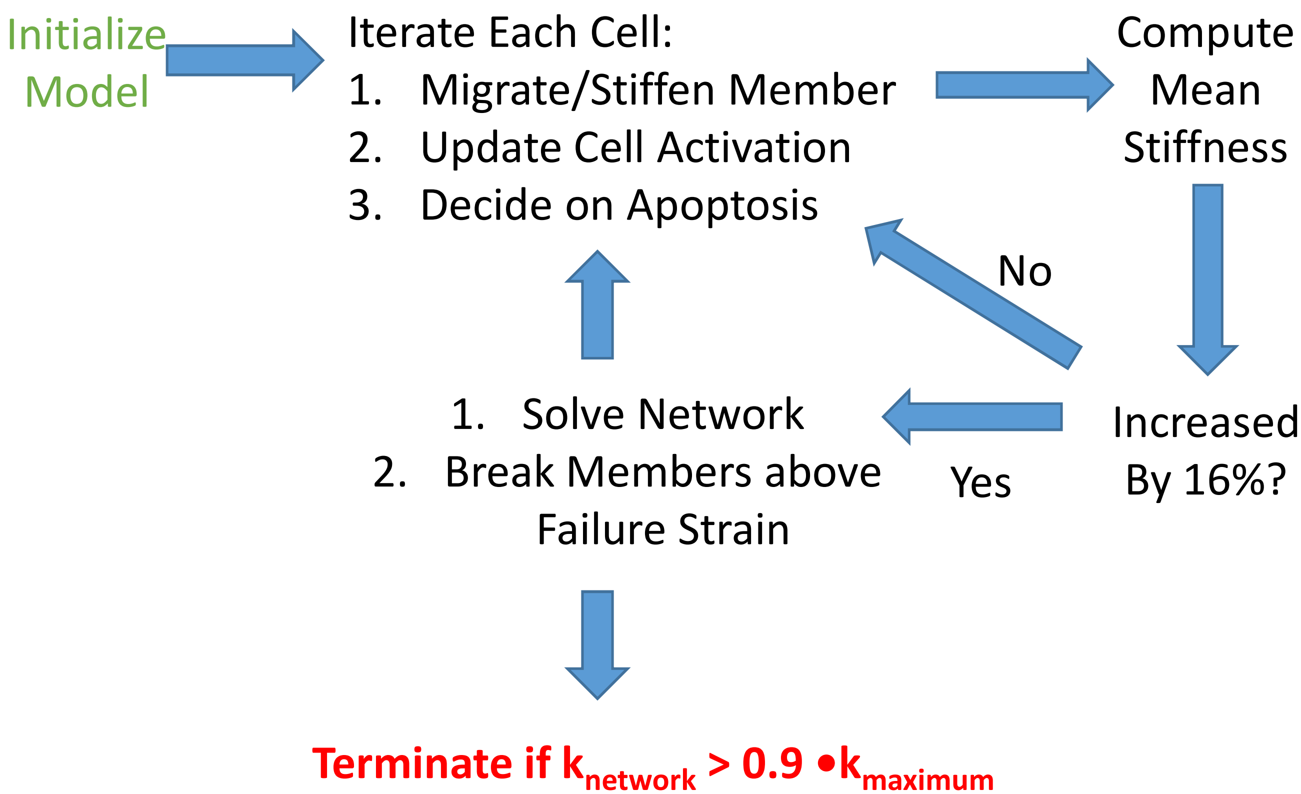
Fibroblast Behavior: Apoptosis

- Fibroblasts from fibrotic lungs show reduced rates of apoptosis (Moodley et al. Am J Respir Cell Mol Biol, 2003).
- Cell death is inversely related to activation level

$$p_{apoptosis} = 0.01*(1 - A/A_{max})$$

  - Dead cell = new cell randomly added to network

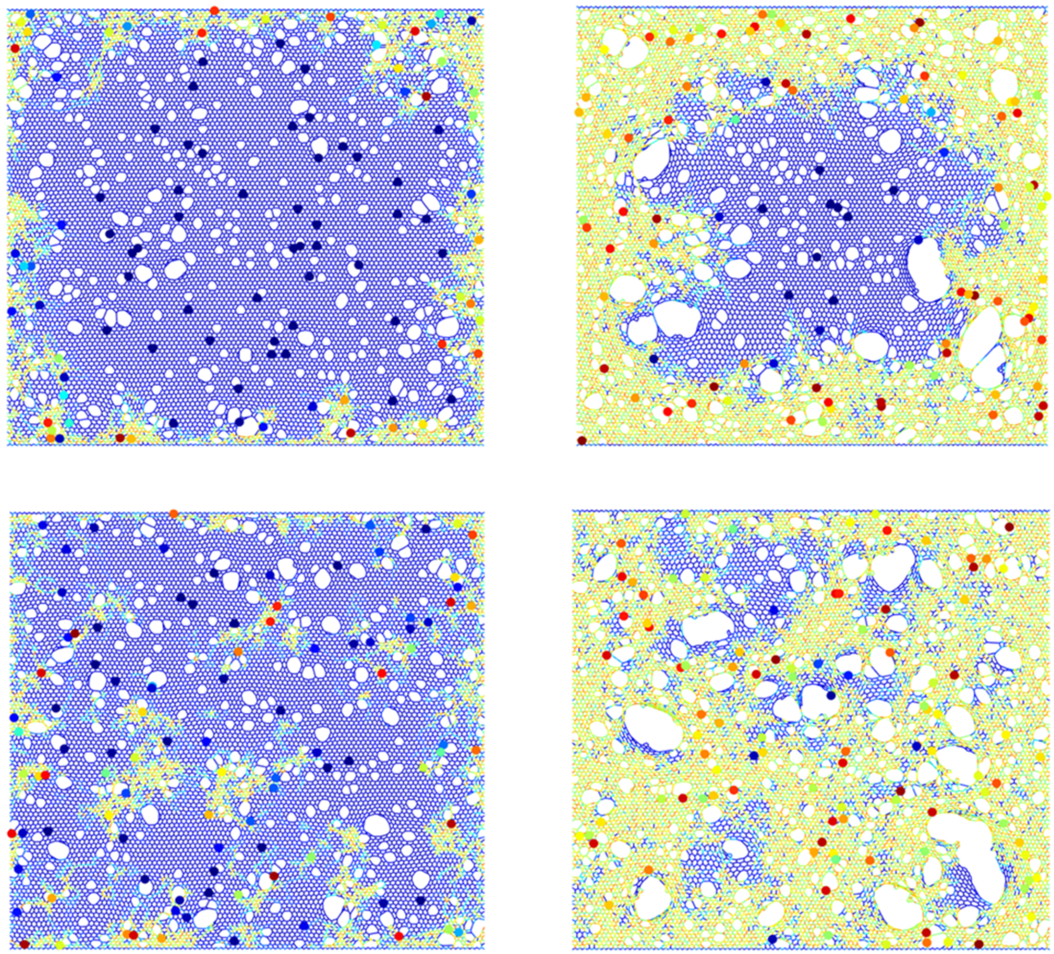
Model Algorithm



Network simulations

Model U: initially unactivated agents

Model A: initially activated agents



Early phase

Late phase

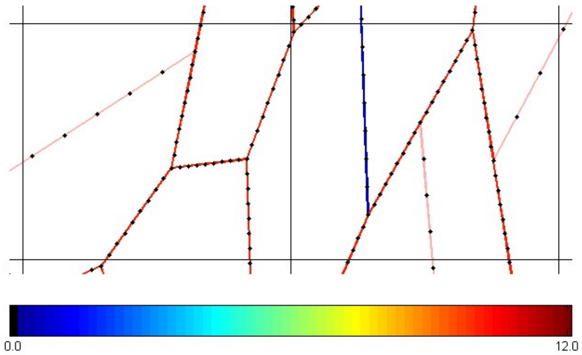
Network color:
Red: high stiffness
Blue: low stiffness

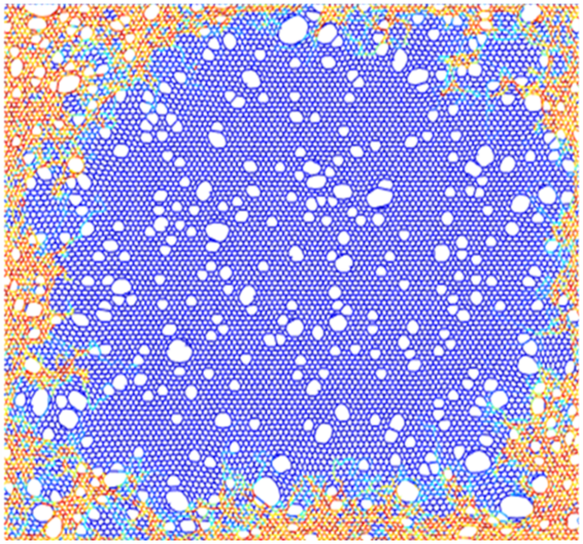
Agent color:
Red: high activity
Blue: low activity

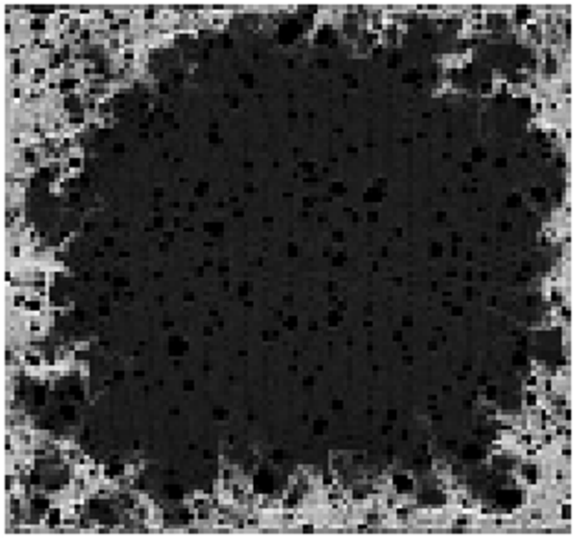
CT Image Simulation

Computation of Pixel Intensity:

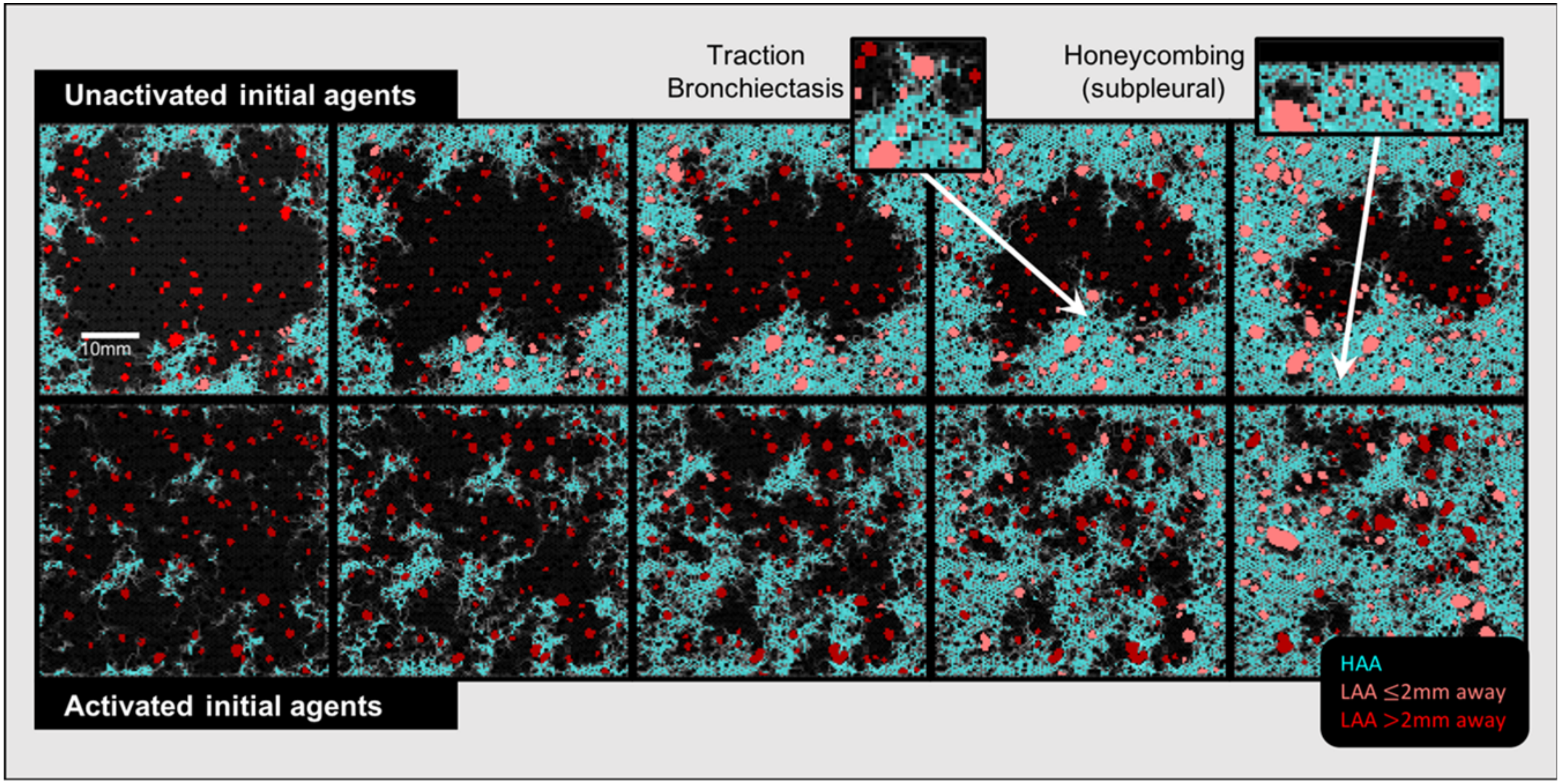
- Discretize each member into 10 points
- Compute k-weighted sum in each pixel:



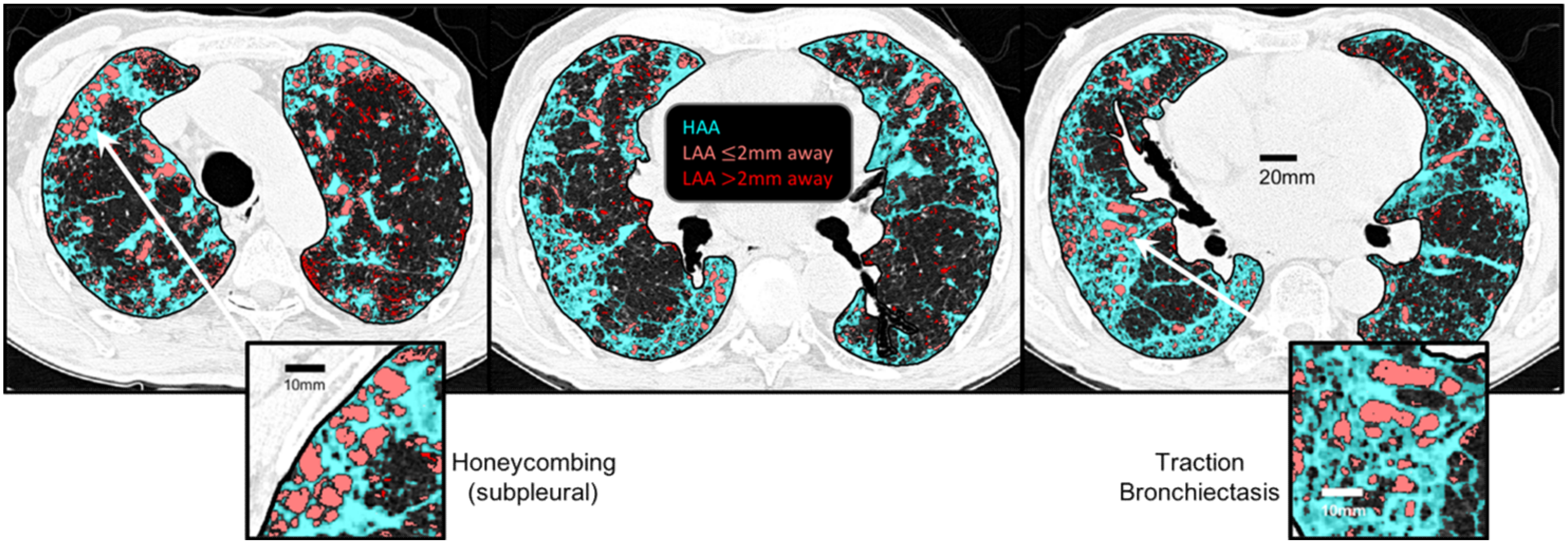




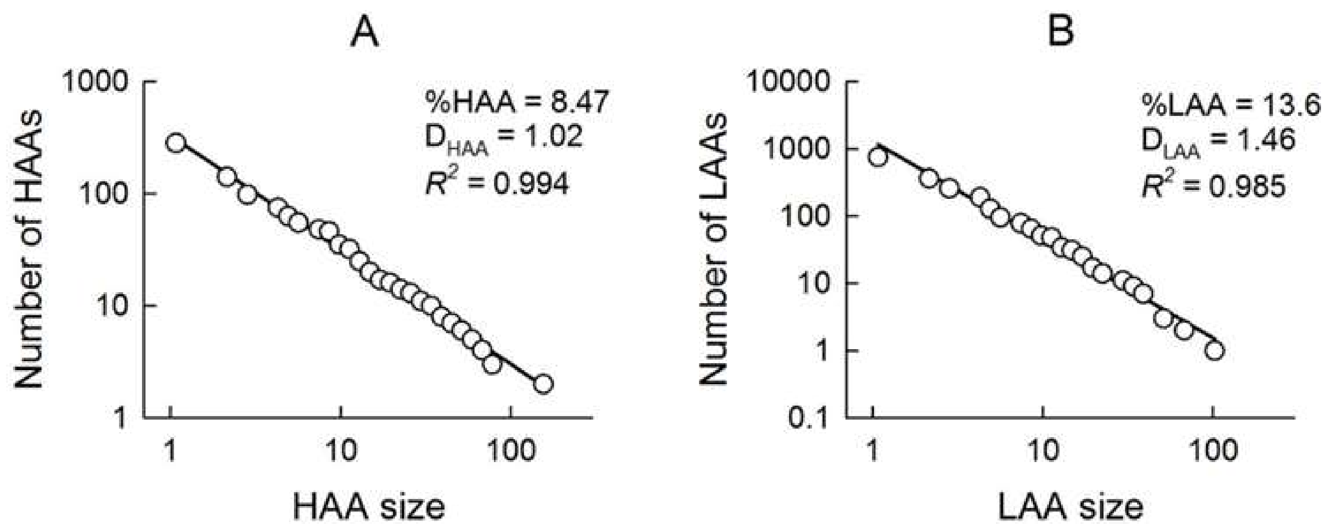
Model-based color coded apparent CT images



Color-coded CT images of human lung fibrosis

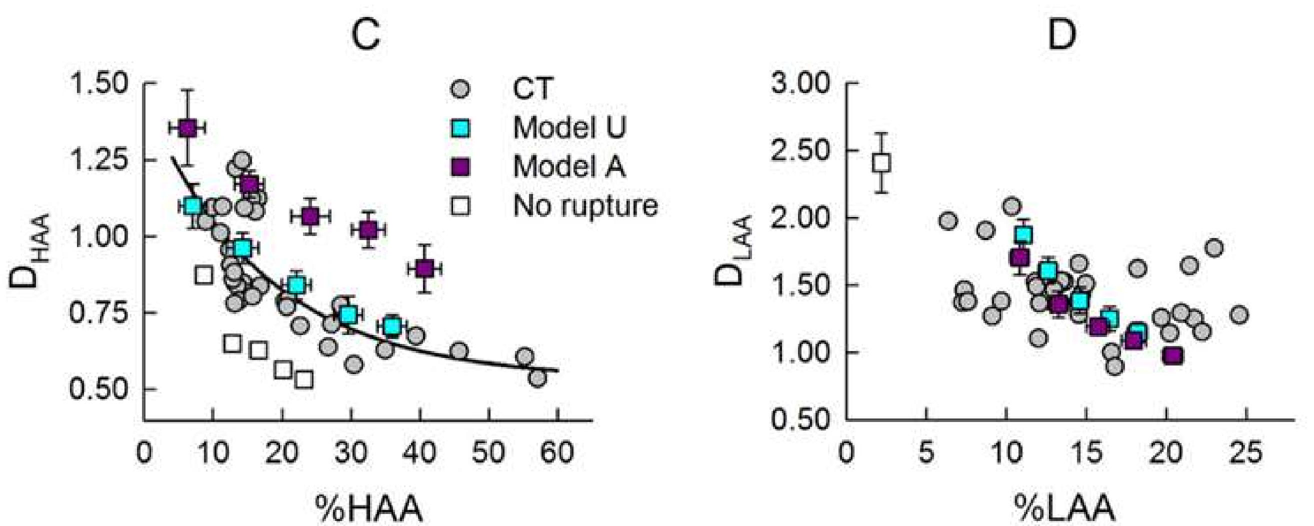


Quantitative comparison



$N_{HAA} \sim HAA^{-D_{HAA}}$

$N_{LAA} \sim LAA^{-D_{LAA}}$



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Conclusions: Fibrosis

- There are two interacting networks:
  - The tissue is a topological elastically coupled network.
  - The cell network contains migrating agents which interact with both the tissue network and itself.
- Stiffness plays a key role in network-network communication.
- Fibrosis arises as a positive feedback loop in the network-network communication.
- Mechanical failure alters topology and is necessary for honeycomb formation.

How to make a network self-healing?

All systems are exposed to degradation, aging, external damage.

A self-healing system must be able to

- recognize damage
- have materials and energy for repair
- initiate the repair upon itself
- recognize when repair is completed.

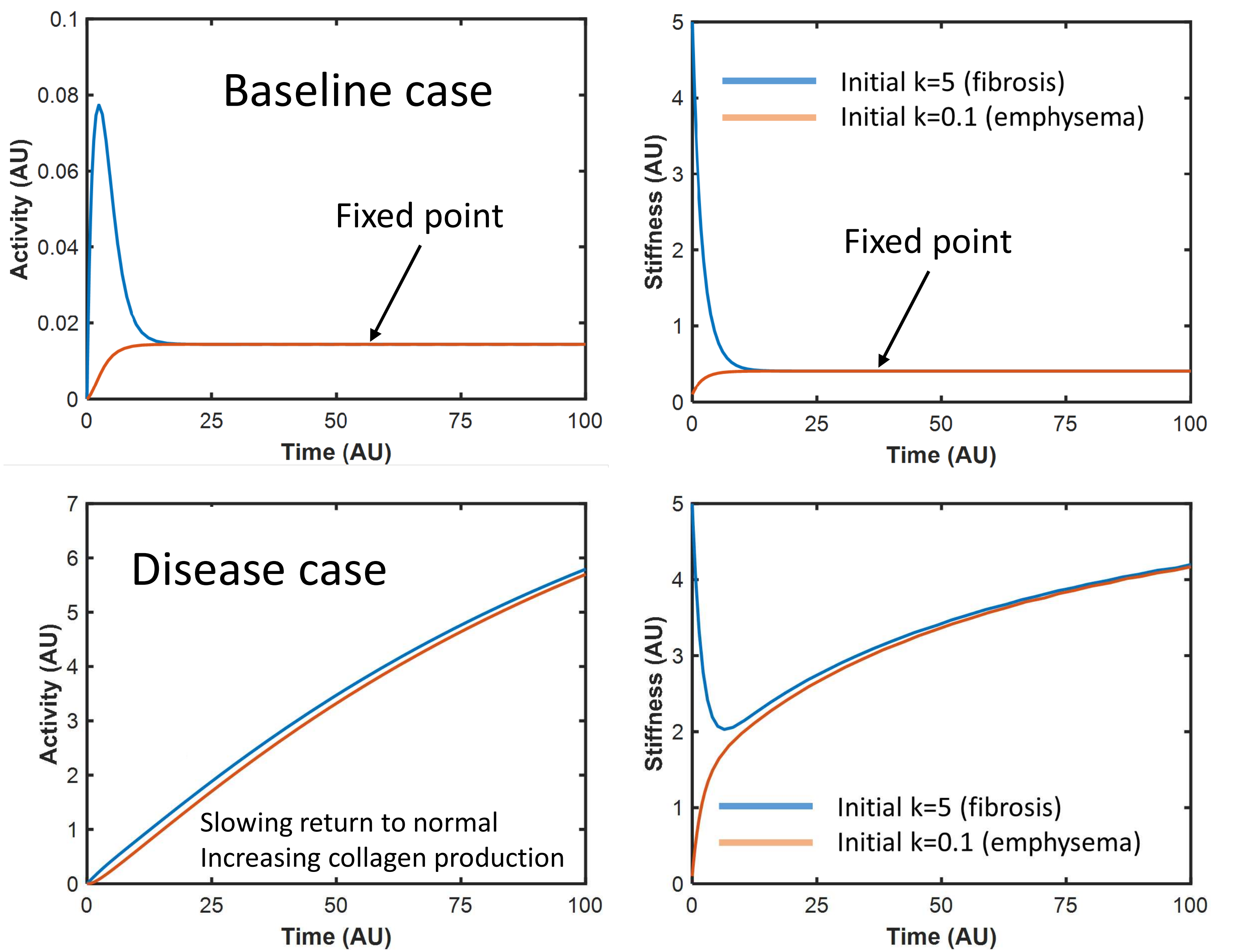
Mathematically, a dynamic system can be self-healing if it has the property to return to a given solution after perturbation. This is called a stable fixed point.

Biologically, a tissue is self-healing if its own cells recognize and repair a damage to return the tissue to its original state.

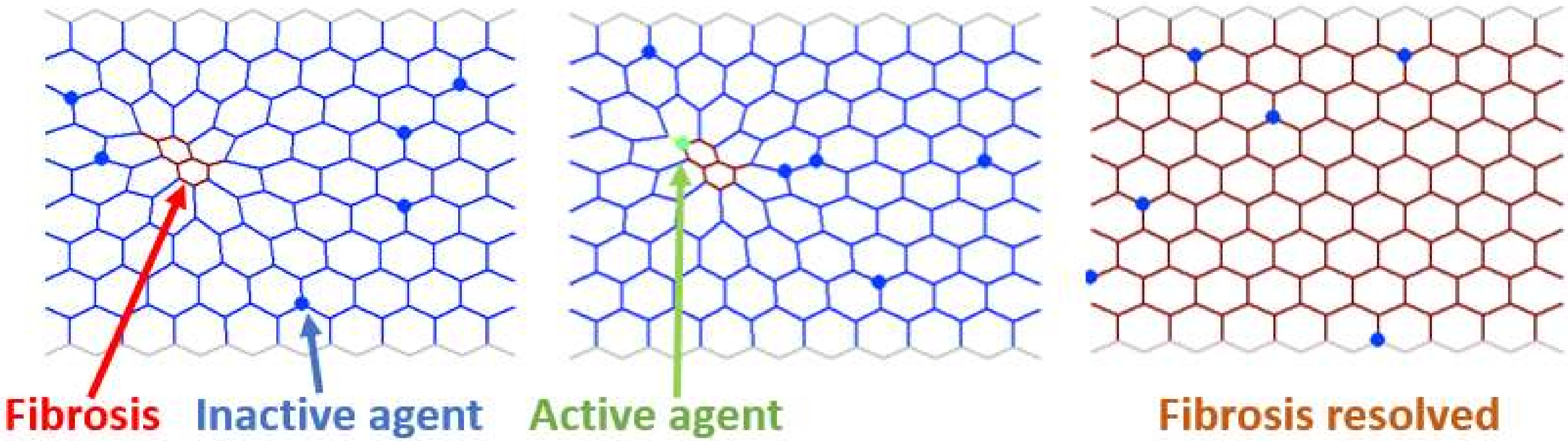
In a biological network, adaptive agents must

- be moving around and search for damage such as abnormal local stiffness
- increase their internal activity when they step on a damaged site
- initiate repair by stiffening or softening
- move on and decrease their activity when stepping on normal site.

Transients approach the fixed points

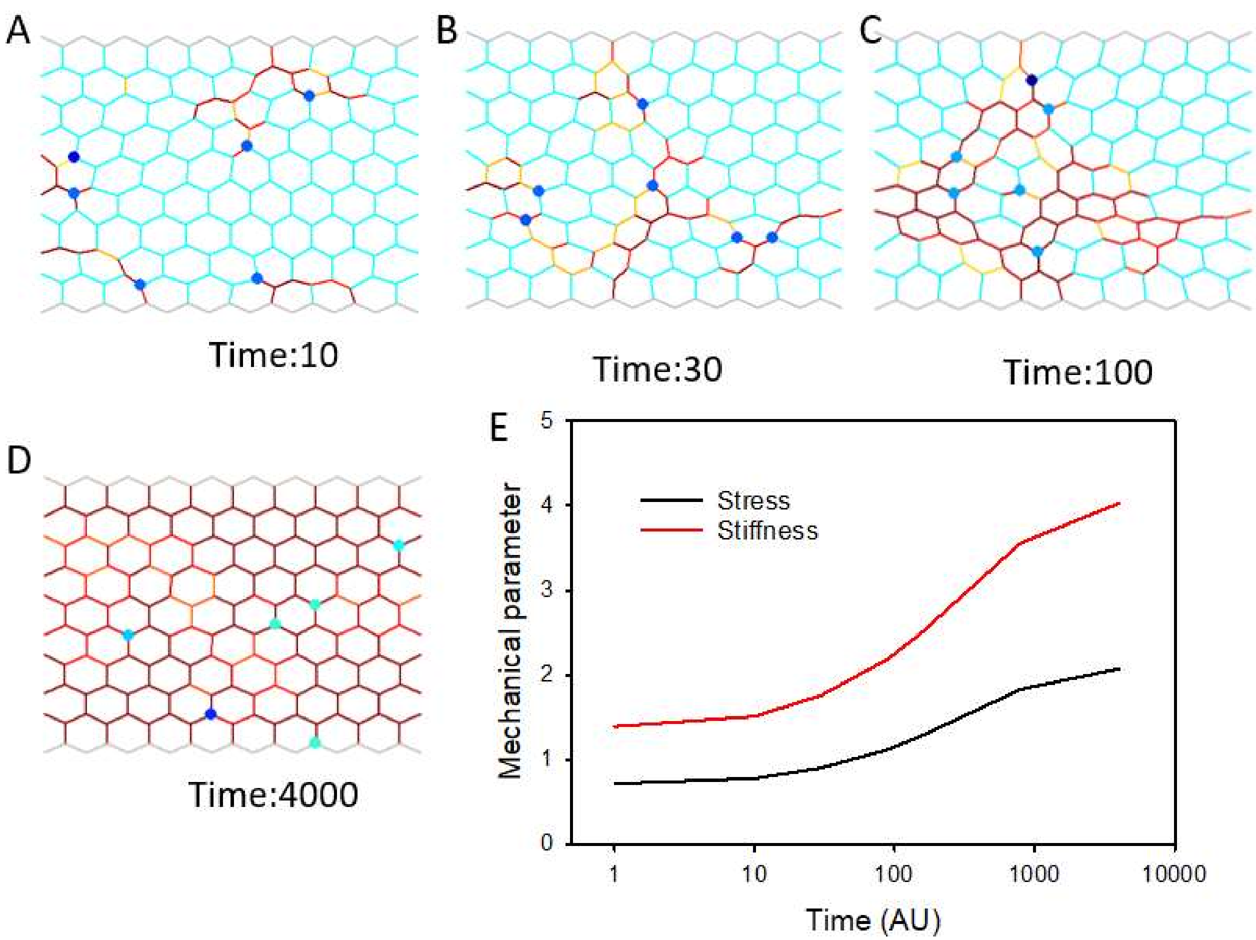


Network implementation of self-healing



Total stress (stiffness) are 0.717 (1.39) and 0.777 (1.52) before (not shown) and after inducing local fibrosis by increasing spring stiffness 7 time (red bonds on left image), respectively. After 10 iterations, an agent (middle, green circle) is activated when it steps on the fibrotic region. After another 2000 iterations, agents visit the fibrotic region many times and the network is self-healed.

Fibrosis develops when self-healing is abnormal



Colors from blue to red on network elements represent increasing stiffness and on agents increasing activity.

Changes in self-healing parameters lead to fibrosis. Panels A, B, C and D show the network and the agents at different time points. Panel E displays the evolution of total stress and stiffness of the network. When α in Eq. 1 describing the attenuation rate of activity is reduced and collagen production rate is increased, the fixed point of each element increases which results in progressive heterogeneous stiffening of the network, similar to pulmonary fibrosis.

Conclusions: Self-healing

- An analytic model has been developed that shows ability of self-healing
- A necessary component of self-healing is that in the equations describing the properties of agents moving around the network have a fixed point.
- The model can serve as a possible mechanisms of tissue homeostasis.
- When network homeostasis fails, it result in progressive disease such as pulmonary fibrosis.